THE ROCKEFELLER UNIVERSITY
1230 YORK AVENUE · NEW YORK, NEW YORK 10021

January 13, 1981

Dr. Joshua Lederberg
President
The Rockefeller University

Dear Josh,

Thank you for the reprints of John Frenster's recent papers.

Frenster's work is hard to appraise. It is primarily theoretical with no strong biochemical base. The major premise is that DNA helix-openings are a measure of localized transcriptional activity; and this is a plausible and defendable thesis. His main probe for helix-openings is the binding of Acridine Orange, usually assessed by fluorescence microscopy. (This is an old technique, made quantitative by Killander and Rigler in the 1960's. When carefully performed it does provide a measure of DNA accessibility in chromatin, but I am not aware of any proof that it can titrate DNA strandedness.) Frenster has also studied the formation of DNA-dye adducts by electron microscopy and autoradiography.

Many of his papers, particularly those presented at meetings, list a variety of compounds which are known to bind DNA (e.g. histones, protamines, carcinogens, dyes, Actinomycin D, etc.) and he correlates that with their inhibition of RNA synthesis. Hypothetical agents that might enhance DNA strand separation (such as "de- repressor RNA's") are invoked as positive effectors in the control of transcription. His published work shows little or no awareness of the remarkable progress in the chromatin field in the last decade - e.g. no mention of nucleosomes, HMG proteins, multiple RNA polymerases or topoisomerases, and no cognizance of the many beautiful EM studies by Miller, Scheer, Foe and others on the structure of transcribing chromatin. Indeed, some observations showing nucleosomes within the transcription unit might be taken as evidence against Frenster's simple view of histones as repressors, and the very best EM studies of transcribing ribosomal genes do not reveal any obvious helix-openings.

The argument for DNA helix-openings would be much stronger for DNA replication, especially with regard to strand separation at the replication fork, but here there are special proteins with DNA-unwinding functions, some of which are well characterized. Frenster's papers rarely if ever mention these biochemical details.

I have known John Frenster since 1963, when we published jointly on the separation of lymphocyte chromatin fractions which differed in template activity for RNA synthesis. He was an interesting and imaginative coworker, but quite uncritical and given to extremes of speculation. Some of his ideas were really original, but he has not kept up with the times. His productivity has been low and few of his papers are published in critically reviewed journals.

To: Dr. Joshua Lederberg
From: Dr. Vincent G. Allfrey
January 13, 1981

Re: John Frenster

He is an active clinician at the Santa Clara Valley Medical Center and is very good with children. In his recent research he has applied the morphometric and staining techniques to the analysis of nuclear changes in eryhrocyte and lymphocyte differentiation. I found his observation that DNA "helix-openings" in immune lymphocytes are asymmetrically distributed in the direction of adjacent neoplastic cells to be especially interesting, and I hope he follows though.

Yours,

Vince

Vincent G. Allfrey